The Nano-Prem: Smaller Presents Big Challenges

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I dedicate this column to the late Dr. Andrew (Andy) Shennan, the founder of the perinatal program at Women's College Hospital (now at Sunnybrook Health Sciences Centre). To my teacher, my mentor and the man I owe my career as it is to, thank you. You have earned your place where there are no hospitals and no NICUs, where all the babies do is laugh and giggle and sleep.

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The resuscitation of infants at ≤23 weeks PMA (referred to as "nano-prems") is a relatively new practice for most clinicians if where they practice offers resuscitation to these babies at all. Aside from the challenges of keeping these babies alive, other factors make it difficult to avoid major morbidities.

The skin of these babies is very immature. Even the electrode gel used for heart monitoring and temperature probe covers used to keep temperature probes in place often produce chemical burns. The result is an increased risk of acquiring infection trans-dermally and undoubtedly is a source of pain for the baby and stress for parents. In addition, fixation rings for transcutaneous monitoring are also unkind to their fragile skin. The adhesive often causes abrasions and skin tearing, while the probes' heat may cause thermal burns.

Given the propensity for bradycardic events common to all premature infants, not monitoring heart rate is not an option. Heart rate can be monitored via a saturation probe, but not all saturation monitors are equally adept at reporting an accurate heart rate, particularly if perfusion is poor. Heart rate can also be taken from an arterial line. ECG electrodes for micro-prems have recently come to market that are less likely to create chemical burns.

The effects of excessively high or low $PaCO_2$ in all premature infants are well known. Large swings in PaCO2 are equally damaging since the resulting changes in cerebral vascular tone result in alterations to cerebral blood flow. This often results in intraventricular hemorrhage. Monitoring a baby's $PaCO_2$ is necessary, and the inability to monitor it non-invasively creates the biggest challenge in ventilating safely.

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Frequent drawing of blood gases and adjusting ventilation help achieve a degree of stasis, but problems are also associated with this practice. A premature infant's circulating blood volume (BV) may vary significantly. One study estimated a BV of 70ml/kg. Packed cell volume (PCV) was an unreliable predictor of blood volume; PCV of 0.41 BV ranged from 50 – 105 ml/kg. Furthermore, other laboratory values are also poor indicators of BV (1). These babies have very little blood to spare, and while delayed cord clamping (DCC) increases circulating volume, it is often impossible due to the baby's status at delivery. The many benefits of DCC are well known (2); the safety and feasibility of placental blood banking for autologous transfusion have been demonstrated (3), although it has not become routine. An added potential benefit is the reduction of retinopathy of prematurity, a topic of current ongoing investigation (3,4). Placental blood banking may become a standard of care, especially when DCC is impossible. Regardless of how much BV is on board, blood sampling for lab work depletes BV like a vampire in a feeding frenzy.

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When an umbilical arterial catheter is in situ, flushing the line after drawing represents a significant amount of total fluid intake (TFI) in a tiny baby, and if normal saline (or even half normal saline) may lead to hypernatremia. Avoiding unnecessary procedural pain during the critical first 72 hours of life is an undeniable benefit to having an arterial line. Because there may be a tendency to draw more blood when an arterial line is available (exacerbating iatrogenic anemia), they should be removed as soon as possible. Capillary sampling avoids the problem of excess TFI and sodium overload, but sampling from tiny heels quickly results in bruising (especially when perfusion is poor), reducing the accuracy of some laboratory measurements.

There are automatic blood measuring systems that result in virtually no blood loss, but these still require about 0.5 mls of flush with each measurement to clear the line. These devices perform well (5) but require indwelling arterial access. Anyone who has inserted umbilical or arterial lines in a sub-500-gram baby can attest that successful placement is far from guaranteed.

Regardless of how blood gases are obtained, they are a snapshot of the baby's state. A baby's position may be changed after a blood gas is drawn. Given the positional nature of endotracheal tubes (especially when orally placed in tiny babies), this may result in a significant increase or decrease in $PaPCO_{2,}$ which will go undetected until the next gas is taken.

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How can we maintain stability in these babies when our most commonly used tool cannot be used? End-tidal CO_2 monitors ($EtCO_2$) are accurate proxies of $PaCO_2$ for trending in the pediatric and adult population, as well as in the neonatal population, albeit with exceptions (6). The validity of $EtCO_2$ in the latter population notwithstanding, several obstacles exist to their use in the NICU.

Patient triggering in the adult world is accomplished either by negative pressure generated by the patient or by flow sensed by the ventilator as a decrease in bias flow. In the neonatal population, the small flow rate and minimal negative pressures a baby generates cannot trigger most ventilators. As technology improves, this may change, but until then, neonatal ventilators rely on flow sensors located at the patient wye. These sensors provide signals for cycle triggering in conventional modes. They also measure volumes to adjust pressure to approximate a requested target volume and calculate leaks around the ETT.

Current $EtCO_2$ monitors utilise infrared absorption technology, either using an inline measuring device or an external device that aspirates gas from the circuit for measurement. Inline devices add significant dead space since they are situated between the ETT and the circuit wye, and devices that aspirate gas from the circuit may interfere with volume and trigger measurement since the volume aspirated will be interpreted as a leak. This can be significant since volume adjustments in volume-targeted modes are as small as 0.1 MLS.

When it comes to high-frequency ventilation, the very small volumes combined with the associated rates in addition to making current EtCO2 medical devices useless. This is a critical obstacle as HFV modes are increasingly used as a first-intention strategy.

CO_2 levels in indoor air have become a hot topic since the arrival of COVID-19, and low-cost monitors to detect it are now widely available. Rather than display partial pressure, these devices display CO_2 measurements in parts per million, typically from 0 to 5000 ppm. It stands to reason that a device sensitive enough to detect CO_2 levels as low as 0 ppm will also detect the difference between ambient bias flow levels and that of ambient gas combined with exhaled tidal volumes, although device response times are likely too slow to measure breath-to-breath changes.

One way around this limitation might be to analyse the CO_2 level in an expiratory gas reservoir and compare this reading to ambient air. Correlation between reservoir readings and $PaCO_2$ measurements taken from blood gases may or may not be demonstrable but could be trended. To my knowledge, this has never been attempted and begs investigation.

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Dissolved CO_2 in water condensate in the expiratory limb of a ventilator circuit and water traps is reflective of $EtCO_2$ (7). CO_2 levels could be trended like gas reservoir analysis. Again, investigation of the feasibility of this method is lacking, but if investigation shows it to be feasible, it offers a potential solution to our current monitoring deficit.

Perhaps the most straightforward solution regarding the $TcPCO_2$ fixation problem would be to find a method of applying the probe without using skin-destroying adhesive rings. Additionally, decreasing the temperature of the heating element should be possible since the immaturity of the nano-prem's skin allows for easier diffusion of CO_2. Decreasing probe temperature also requires clinical validation.

Medical devices are expensive to bring to market, and the nano-

prem population is likely too small to make developing a new monitor profitable for a company. Finding a friendlier fixation device represents the least expensive and most elegant solution.

The ingenuity of bedside clinicians (can you say "Respiratory Therapists?") has long been a source of discovery. The task at hand is awaiting our ingenuity and acceptance of the challenge.

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